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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,631	01/16/2003	Charlotte Hauser- Funke	KGB	3848

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,631	HAUSER- FUNKE, CHARLOTTE	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-115* is/are pending in the application.

4a) Of the above claim(s) *50-70,77-105 and 108-115* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-76,106 and 107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the Restriction was received on 3/11/2005. Claims 50-115 are pending in the instant application. Applicant's election with traverse of Group II, claims 71-76, drawn to a nucleic acid construct comprising an HRE and a transgene encoding a blood clotting factor, which are not functionally linked, compositions comprising the nucleic acid construct, and methods of making of such compositions, and the species of Factor VIII in the reply filed on 1/05/2005 is acknowledged. It is noted that claims 75 and 76 continue to read on the unelected subject matter of group I. Applicant amended claims 50, 53-56, 60, 62, 65, 70, 72, 75, 77-78, 83, 87, 91, 93, and 97; new claims 99-113 were added. The new claim groupings are now Group I, claims 50-70, 75-79, 99-105, 114, and 115; Group II, claims 71-76, 106 and 107; and Group III, claims 83-98, 108-113. Please note that the examiner of record is now Dr. Louis D. Lieto of ART UNIT 1632.

Claims 50-70,77-105 and 108-115 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/10/2005.

Applicant argues that the special technical feature shared by all of the claims on Groups I-III is the nucleic acid construct comprising at least one HRE and a transgene. US Patent No. 5,756,264 and US Patent No. 5,298,422 disclose a nucleic acid construct comprising at least one HRE and a transgene. US Patent No. 5,756,264 discloses a nucleic acid construct which has a response element consisting of at least one Vitamin D response element (claim 21) and a transgene encoding a human clotting factor, such as factor IX or factor VIII (pgph 64). US Patent

No. 5,298,422 discloses a nucleic acid construct, which has a response element consisting of at least one Vitamin D response element (claim 27) and a transgene encoding a human blood clotting factor (pgph 28). Since the said common technical feature of the nucleic acid construct comprising at least one HRE and a transgene was known from the prior art documents US Patent No. 5,756,264 and US Patent No. 5,298,422, the subject matters of claims 50, 71, 83 and 114 are not so linked as to form a single general inventive concept (Rule 13.1 PCT) as they appear not to be linked by a new and inventive common special technical feature in the sense of Rule 13.2 PCT by taking into account the state of the art.

The requirement is still deemed proper and is therefore made FINAL.

Claims 71-76, 106 and 107 are currently under examination.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) and applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) is acknowledged.

Information Disclosure Statement

The references submitted have been considered, but will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO/SB/08A and 08B form, must be filed within the set period for reply to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 71-76, 106 and 107 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The claims encompass a nucleic acid construct comprising at least one hormone response element (HRE) and a transgene encoding a blood clotting factor, such as Factor VIII, wherein at least one HRE is not functionally linked to the transgene. Wherein the nucleic acid construct may be contained within a vector or comprised within a cell or organism.

The specification, while providing guidance on the design and construction of a plasmid comprising a nucleic acid construct containing a progesterone response element (PRE) and a sequence encoding the blood clotting factor, does not teach the construct is capable of being used as intended. The Specification teaches that the intended use of the nucleic acid construct containing PRE and encoding a blood clotting factor, Factor VIII is to treat a blood clotting disorder, such as hemophilia, by administering a therapeutically effective amount of the construct to an organism (Specification pg. 23, lines 1-6; pg. 25 lines 3-10). The sole working example disclosed, describes the administration of a plasmid containing a nucleic acid construct by oral or intramuscular injection, which contains a PRE and sequence encoding human Factor

IX, under various conditions to male C57BL/6 mice (Example 9, pg. 41). However, the results of the experiment disclosed in Figures 17 and 18 fail to show any statistical differences in the blood coagulation time. Figure 17 shows that the error bars of control group 1 (without plasmid) extensively overlap the values obtained for all of the test groups, despite differences in route of administration or composition, indicating that there is no statistical difference between the groups. Further, Figure 18 shows that on days 3 and 8 group 1 had the longest blood coagulation time of any of the test groups. This indicates that either successful gene transfer was not established, that the plasmid containing the nucleic acid construct was unable to express adequate levels of human factor IX over the time frame observed, or that expression of human factor IX in mice does not have a consistent effect on blood coagulation time. Together the results presented in Figures 17 and 18 indicate that the nucleic acid construct has no predictable effect on blood clotting time in mice, in comparison with untreated mice.

Further, Verma et al. states that in general, the Achilles heel of gene therapy is gene delivery, and that, most of the approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, column 3, paragraph 2}. Marshall concurs, stating that, difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field, and that, many problems must be solved before gene therapy will be useful for more than the rare application {Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1}. Orkin et al. further states in a report to the NIH that, none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated, and that, while the expectations and the promise of gene therapy are

great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol {Orkin et al. (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2}. Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, and the need for appropriate vector/promoter combinations for a particular cell type. In regards to the latter issue, Verma states that, the search for such combinations is a case of trail and error for a given cell type {Verma, (1997) Nature, 389, page 240}. Given the teachings in the specification that a plasmid containing a nucleic acid construct, which contains a PRE and sequence encoding human Factor IX has no affect on blood clotting time in comparison to a control mouse, regardless of the composition or route in which it was administered, the absence of any other working examples disclosing the administration of a nucleic acid construct containing any HRE and any other blood clotting factor, and the teachings in the art that methods of gene therapy remain unpredictable methods of treatment, the skilled practitioner would be unable to predict how to practice the claimed invention without undue and extensive experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 71-76, 106 and 107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 71-76, 106 and 107 refer to a nucleic acid construct comprising at least one HRE that "is not functionally linked" to a blood clotting factor. The term "is not functionally linked" could mean not physically linked or that the HRE has no effect on the transgene, and is vague and indefinite. The term "is not functionally linked" is not defined in the specification and is confusing, given that HRE elements are known in the art to function as enhancers. It is unclear if applicant intends that the claimed HRE has absolutely no role in regulating transcription of the blood clotting factor, or if it may have a regulatory role, in which case it is functionally linked to the blood clotting factor. The metes and bounds of claim 71 cannot be determined. Claims 72-76, 106 and 107 depend on claim 71.

Claims 75 and 76 refer to a "composition of matter". The term "composition of matter" encompasses elemental particles such as protons, neutrons and electrons. It is unclear if applicant intends such elemental particles or higher structural organizations of matter, such as atoms and molecules. Therefore the metes and bounds of claims 75 and 76 cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claims encompass a nucleic acid construct comprising at least one hormone response element (HRE) and a transgene encoding a blood clotting factor, such as Factor VIII, wherein at

least one HRE is not physically linked to the transgene. Wherein the nucleic acid construct may be contained within a vector or comprised within a cell or organism.

Claims 71, and 73-76 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S Patent No 5,298,422 (1994), hereafter referred to as Schwartz[1] et al.

Schwartz[1] et al. provides guidance on a nucleic acid construct, which has a response element consisting of at least one steroid response element, such as the Vitamin D response element (claim 27), which is not is not functionally linked to the transgene (Figure 3) and a transgene encoding a blood clotting factor (col. 8, lines 10-15). Further Schwartz[1] et al. teaches that the construct can be introduced into a host organism or host tissue using a vector, such as a plasmid or cosmid (col. 6, lines 25-30). Therefore, the disclosure of Schwartz[1] et al. meets all of the limitations of the above rejected claims.

Claims 71-76, 106 and 107 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S Patent No US Patent No. 5,756,264 (1998), hereafter referred to as Schwartz[2] et al.

Schwartz[2] et al. provides guidance on a nucleic acid construct, which has a response element consisting of at least one steroid response element, such as the Vitamin D response element (claim 21), which is not is not functionally linked to the transgene (Figure 11) and a transgene encoding a human clotting factor, such as Factor IX or Factor VIII (col. 8, lines 65-67; and col. 13, lines 45-60). Further Schwartz[2] et al. teaches that the construct can be introduced into a host organism or host tissue using a vector, such as a plasmid, cosmid, or virus (cols 3 lines 15-60 and 7, lines 60-65). Further, Schwartz[2] teaches a composition comprising the nucleic

acid construct, Vitamin D and the Vitamin D receptor (Figure 13). Therefore, the disclosure of Schwartz[2] et al. meets all of the limitations of the above rejected claims.

No Claims Allowed

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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